Highlights

1. Addictive drugs target molecular mechanisms of synaptic plasticity in the cerebellum
2. Drug-dependent changes in the cerebellum go beyond homeostatic alterations
3. Drug-related cue memories also involve the cerebellum
4. Instrumental memory and executive functions recruit cerebellar circuits
5. **Cerebellar alterations are present in many comorbid neuropsychiatric disorders**

Have we been ignoring the elephant in the room?

Seven arguments for considering the cerebellum as part of addiction circuitry

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Abstract

Addiction involves alterations in multiple brain regions that are associated with functions such as memory, motivation and executive control. Indeed, it is now well accepted that addictive drugs produce long-lasting molecular and structural plasticity changes in corticostriatal-limbic loops. However, there are brain regions that might be relevant to addiction other than the prefrontal cortex, amygdala, hippocampus and basal ganglia. In addition to these circuits, a growing amount of data suggests the involvement of the cerebellum in many of the brain functions affected in addicts, though this region has been overlooked, traditionally, in the addiction field. Therefore, in the present review we provide seven arguments as to why we should consider the cerebellum in drug addiction. We present and discuss compelling evidence about the effects of drugs of abuse on cerebellar plasticity, the involvement of the cerebellum in drug-induced cue-related memories, and several findings showing that the instrumental memory and executive functions also recruit the cerebellar circuitry. In addition, a hypothetical model of the cerebellum's role relative to other areas within the corticostriatal-limbic circuitry is also provided. Our goal is not to review animal and human studies exhaustively but to support the inclusion of cerebellar alterations as a part of the physiopathology of addiction disorder.

Notwithstanding the enormous progress having been made during the last decade in the knowledge of neurobiological mechanisms in drug addiction, there are still many gaps and unenlightened points that need to be elucidated. It is now well accepted that addictive drugs produce long-lasting molecular and structural plasticity alterations in the corticostriatal-limbic circuitry (Kalivas et al., 2005; Hyman et al., 2006). However, there are brain regions that might be relevant to addiction other than the prefrontal cortex, amygdala, hippocampus and basal ganglia. An increasing amount of data suggests the involvement of the cerebellum in many of those brain functions affected in addicts. However, this structure has been traditionally disregarded in the addiction field. Why should we consider the cerebellum? The present review is an attempt to provide the arguments to encourage the inclusion of the cerebellum in the drug addiction circuitry. We do not intend to review exhaustively animal and human studies as this has already been done elsewhere (Miquel et al., 2009; Moulton et al., 2014).

A summary of the functional anatomy and synaptic interactions in the cerebellum

It is astonishing to realize how many dogmas about the cerebellum have been challenged in the last few decades. This is so not only when regarding cerebellar functions but also cerebellar evolution and anatomy. In two enlightening papers (Azevedo et al., 2009; Lent et al., 2012), the authors showed the cerebellum contains 80% of all the cerebral neurons squeezed into only 10% of the whole brain mass. The total human brain mass is 1,232g, wherein some 77 billion cells are packed. Only 16 billion of these cells are neurons. However, the human cerebellum alone comprises 80 billion cells in a mass of 154g; 60 billion are neurons. Therefore, the cerebellum includes a much higher number of neurons and a lower amount of glia cells than the brain. Moreover, in mammals the evolution of cerebellar size has covaried with the cerebral cortex (Herculano-Houzel et al., 2006). If we accept that function depends on structure, this little brain would be more relevant with regard to explaining brain functions than we have previously thought.

The clinical and experimental observations in the 19th century contributed to establishing the

view of the cerebellum as being exclusively related to motor functions (Ramnani, 2006; Glickstein et al., 2011). From the very beginning, it was clear that coordination was the main cerebellar motor function. However, also by this time other roles were proposed. For example, phrenologists considered the cerebellum to be responsible for sexuality and sexual misbehaviour (Glickstein et al., 2011). As a curiosity, more than a century later research in other mammals and humans has consistently supported the involvement of the cerebellum in sexual behaviour (Holstege et al., 2003; Holstege and Huynh, 2011; Manzo et al., 2008; Garcia-Martinez et al., 2010; Paredes-Ramos et al., 2011). Nowadays, growing evidence has confirmed the participation of the cerebellum in a broad spectrum of functions. This evidence derives from animal research as well as correlational and human clinical studies. Examples of these unexpected roles are cerebellar involvement in emotional memory and emotional experience (Sacchetti et al., 2002; Sacchetti et al., 2004; Schutter and van Honk, 2006; Baumgartner et al., 2006; Turner et al., 2007); language (Leiner et al., 1993); planning, prediction and temporal perception (Courchesne and Allen, 1997; Bastian, 2006; Kotz et al., 2014; Legio and Molinari, 2015); automatisation of rules (Balsters and Ramnani, 2011) or decision making (Moers-Hornikx et al., 2009; Rosembloom et al., 2012; Gabay et al., 2014). Remarkably, many of these brain functions are those that have been demonstrated to be altered in addicted patients and in individuals suffering comorbid mental disorders.

The cerebellum is an evenly shaped structure with a unique stereotyped neuronal organization (Ramnani, 2006). The cerebellar geometry is like a hemispherical ellipse with a central region called the vermis and two hemispheres on each side (Larsell, 1952). The cerebellar outline has a wavy form in the rostro-caudal orientation, which results from the presence of transverse fissures. The arrangement of fissures in the cerebellar cortical surface allows the identification of 10 different lobules **(Figure 1).** Each of these lobules has been linked to specific brain-cerebellar functional loops (Voogd and Glickstein, 1998; Bostan et al., 2013). From a dorsal-ventral view, the cerebellar cortical array shows three clearly identified layers **(Figure 2).** The molecular layer includes Purkinje dendritic arborisation and inhibitory interneurons (basket

and stellate cells). Ventrally, the Purkinje layer is formed by Purkinje somas and Bergman glia. At the deeper cortical level, the granular layer contains a huge number of granule cells modulated by Golgi (Eccles et al., 1964), unipolar brush cells and Lugaro neurons, as well as different types of glia (see Cerminara et al., 2015 for a recent review). Ascending granule cell axons bifurcate into excitatory parallel fibres contacting Purkinje somas and dendrites. The cerebellar cortex receives only two excitatory inputs (Marr, 1969; Albus, 1971; Gilbert and Thach, 1977). Neuronal information from cerebral cortices, limbic areas and basal ganglia reaches the cerebellum through mossy fibers (MF) originating in the pontine nuclei. Climbing fibers (CF), which arise from the inferior olive and climb up to dendrites of one Purkinje neuron provide the other excitatory input. These two excitatory inputs control the Purkinje's inhibitory output onto neurons of the deep cerebellar nuclei (DCN) (Ito 1984). The activation of glutamatergic neurons in the deep cerebellar nuclei (DCN) releases the information out of the cerebellum.

Seven arguments for considering the cerebellum as a part of addiction circuitry

For years the cerebellum was only seen as being related to drug-induced homeostatic adaptations (tolerance and physical dependence) that may occur within cells and circuits after repeated stimulation (Edwards and Rizk, 1981). Both tolerance and physical dependence were considered to be primary symptoms of addiction. In fact, for the psychiatrist community, it was not until the current version of the Manual of Mental Disorders (DSM-5) appeared, that it was finally acknowledged that these two symptoms are not sufficient for a person to be an addict. The current approach to addiction disorder hereby proposes that addiction would involve a motivational syndrome featured by both a compulsive pattern of drug consumption and high risk of relapse as the two major symptoms of the disease (Robinson and Berridge, 1993; Everitt and Robbins, 2005; Hyman et al., 2006; Everitt, 2014). The transition from a recreational use of drugs to a compulsive phenotype of drug seeking and drug taking results from drug-induced long-term changes in the corticostriatal-limbic circuitry in a way that rewires these circuits

(Everitt and Robbins, 2005; Kalivas et al., 2005; Hyman et al., 2006). Rewiring involves a structural and functional reorganization that follows a ventral-dorsal gradient (Everitt and Robbins, 2005; Corbit et al., 2012; Willuhn et al., 2012; Murray et al., 2013). A similar pattern has been proposed to sustain consolidation of instrumental memory (Yin and Knowlton, 2006). In the following pages we will try to summarise and discuss the seven reasons as to why the cerebellum should be considered as a part of the circuitry responsible for undergoing long-lasting drug-induced behavioural effects.

1. Widespread projections connect the cerebellum to the corticostriatal-limbic circuitry.

The proposal of anatomical and functional loops between striatum-cortico-limbic circuits and the cerebellum has been supported by numerous studies since four decades ago (see Bostan et al., 2013 for a review). These studies have delineated anatomical connections between these apparently segregated networks. Thus, there are two pathways to connect cerebellum and prefrontal cortex (PFC) (Rogers et al., 2011). The first network involves the dentate/lateral nucleus, reticulo-tegmental nuclei, pedunculopontine nuclei and ventral tegmental area and finally the mPFC. The second is from the dentate nucleus via mediodorsal and ventrolateral thalamus. Furthermore, a dopaminergic direct ventral tegmental area (VTA)-cerebellar projection has been demonstrated (Ikai et al, 1992; Ikai et al., 1994). Detectable DA levels were found in posterior lobules of the vermis VII–X, right and left hemispheres and the fastigial, dendate and interpositus deep nuclei (Glaser et al., 2006). In addition, the cerebellar cortex regulates dopamine release in the medial prefrontal cortex by two independent glutamatergic pathways. One of them reaches the VTA through reticulotegmental and pedunculopontine nuclei (Forster and Blaha, 2003). The other one arrives at VTA through mediodorsal and ventrolateral thalamus (Rogers et al., 2011).

Other studies have confirmed functional relationships between the cerebellum and striatal-cortico-limbic circuitry. For example, acute stimulation of SNc (Substantia Nigra pars compacta) by picrotoxin increases cFOS expression in the vermis and cerebellar hemispheres

(Herrera-Meza et al., 2014). Also, this relationship is revealed after injury or alteration. Right hemicerebellectomy prevents contralateral striatal LTD (Rossi et al., 2008). The degeneration of the nigrostriatal dopaminergic pathway that occurs in Parkinson's disease (PD) induces a hyperactivation of the cerebellum (Yu et al., 2007). Moreover, administration of the neurotoxine 1-methyl-4-phenyl-1,2,3,6- tetrahydropyridine (MPTP) to primates to produce a nigrostriatal degeneration induced a persistent activation of the Purkinje neurons that correlated with the degree of dopamine loss (Heman et al., 2012). Interestingly, after chronic treatment with haloperidol, cFOS expression in the vermis was opposite regulated to that observed in the cerebellar hemispheres (Herrera-Meza et al., 2014). Indeed, chronic systemic haloperidol increases cFos expression in the cerebellar hemisphere but decreases such expression in the vermis.

Cerebellar microcircuits also form functional networks via the thalamus with the septo-hippocampal complex and the amygdala (Sacchetti et al., 2002; Sacchetti et al., 2005). In fact, cerebellar stimulation evokes neuronal activity in the amygdala and hippocampus (Heath et al.,1978). Altogether, findings strongly suggest functionally interconnected cerebellar-striatal-cortico-limbic networks.

2. Addictive drugs target the main molecular mechanisms of synaptic plasticity in the cerebellum.

After several decades of research on neurobiological underpinnings of addiction, it is beyond doubt that plasticity alterations in glutamatergic synapses regulated by dopamine and a plethora of other neuromodulators are the final result of repeated experience with addictive drugs (Gipson et al., 2014; Loweth et al., 2014). It is through several functional and structural modifications in these synapses that drugs are able to reorganize the corticostriatal-limbic circuitry. As has been illustrated by a number of studies, short- and long-term plasticity in cerebellar synapses are both mediated by glutamate and endocannabinoid-dependent cellular mechanisms (Ito, 1984; Batchelor and Garthwaite, 1993; Salin et al., 1996; Chevaleyre et al.,

2006). Moreover, it is known that the vermis receives dopaminergic projections from the VTA (Ikai et al, 1992; Ikai et al., 1994) and expresses dopamine transporters (DAT) (Melchitzky and Lewis, 2000; Carbo-Gas et al., 2014a). Drug-induced molecular mechanisms in the cerebellum have been extensively revised and discussed previously (see Miquel et al., 2009 for a review). Overall, addictive drugs modify cerebellar glutamate and endocannabinoid interactions (Netzeband et al., 1999; Rubino et al., 2004; Palomino et al., 2014), neuromodulators like norepinephrine and dopamine (Ferrucci et al., 2007; Yin et al., 2010; Bekheet et al., 2010), intracellular signalling transduction pathways (Sanna et al., 2002; Alfonso-Loeches and Guerri, 2011), as well as gene expression (Enoch et al., 2014; Palomino et al., 2014). Several of these drug-induced molecular changes have been correlated with drug tolerance, drug dependence and the withdrawal syndrome (Hutcheson et al., 1998; Sanna et al., 2002; Rubino et al., 2004; Vinod et al., 2006).

3. Drug-dependent changes in the cerebellum go beyond homeostatic alterations.

All drugs with an addictive potential have been shown to produce behavioural sensitisation; it is a progressive increase in drug-induced stimulating and incentive effects (see Robinson and Berridge, 2008 for a review). The final behavioural output results from the up-regulation of several intracellular pathways and long-term changes in the dopaminergic and glutamatergic system strongly stimulated by addictive drugs (see Leyton and Vezina, 2013 for a review). Sensitisation may reinforce associations between conditioned cues and drug effects leading to an enhancement of conditioned memories (Vezina, 2004). It is in this way that incentive sensitization contributes to intensifying craving and drug seeking.

Several molecular changes have been observed in the rodent cerebellum after the development of psychostimulant sensitisation. A cocaine-sensitised regimen increases the binding of MK-801, an NMDA antagonist in the cerebellum (Bhargava and Kumar, 1999). Furthermore, sensitisation of cfos and junB mRNA expression have been demonstrated in the cerebellar cortex of cocaine-sensitised rats. This effect is mediated by D1, D2, $GABA_B$ and NMDA

cerebellar receptors (Couceyro et al., 1994; Klitenick et al., 1995). Interestingly, glutamate-endocannabinoid synaptic interactions within the cerebellum have been also associated with cocaine-induced sensitisation (Palomino et al., 2014). Very recently, we have investigated molecular and structural plasticity in the cerebellum of sensitized mice (Vazquez-Sanroman et al., 2015a; Vazquez-Sanroman et al., 2015b). One of the main conclusions derived from this research is that cocaine promotes plasticity in the cerebellum in a similar way to that previously reported in the basal ganglia (Robinson and Kolb, 1999; Robison and Berridge, 2001; Fumagalli et al., 2007). After six cocaine injections, we included either a withdrawal period of one week or a withdrawal period of one month; then followed by a new cocaine challenge. Remarkably, drug-induced cerebellar plasticity in sensitised mice appears to depend on the length of the withdrawal time. After a short period of withdrawal, a new cocaine injection promoted an accumulation of proBDNF and higher levels of its receptor $p75^{NGFR}$ to the detriment of matureBDNF mechanisms. Cocaine-dependent accumulation of proBDNF was mainly seen in Purkinje neurons that also expressed high levels of the GluR2 AMPA subunit, apparently being internalized in Purkinje dendrites. Interestingly, these changes were associated with pruning in the dendritic spines and, a reduction in size and density of the Purkinje synaptic terminals. Overall, a chronic regimen of cocaine followed by a one-week withdrawal period led to a reduction in the Purkinje inhibitory control on the DCN neurons. Accordingly, Purkinje neurons exhibited less cFOS expression after the last cocaine challenge. As expected, DCN neurons receiving the inhibitory Purkinje input showed higher activity. Moreover, the perineuronal nets surrounding the soma of DCN projection neurons were stronger in sensitised animals, reducing the probability for structural remodelling in the Purkinje-DCN synapses (Vazquez-Sanroman et al., 2015a). When a withdrawal period of one month preceded the last cocaine injection (Vazquez-Sanroman et al., 2015b), the cerebellar plasticity observed in sensitised mice was substantially different from the previous observations. In this case, proBDNF and mature-BDNF levels were both enhanced by cocaine. We also found an increase in GluR2 expression, but after preventing the penetration of the antibody, the GluR2 signal was significantly reduced

in the dendritic tree of all lobules except lobule IX. Moreover, dendritic sprouting and increased bouton size in Purkinje neurons accompanied a high BDNF and GluR2 expression. Additionally, we found a reduction in extracellular matrix components surrounding projection neurons in the DCN that might facilitate the subsequent remodelling of Purkinje-DCN synapses.

Hence, when taken together, these findings provide evidence that the same dose and number of cocaine administrations are capable of challenging cerebellar plasticity very differently, only by extending the withdrawal time. During short-withdrawal periods, Purkinje neurons seemed to reduce their capability of inhibiting DCN neurons, whereas during long periods of withdrawal, dendritic and axonal remodelling of Purkinje followed a different trend. In this case, Purkinje neurons increase their input and output strength in sensitised animals. Similar plastic modifications have been described in the striatum and linked to the incubation of craving after long periods of withdrawal (Loweth et al. 2014). Nevertheless, a causal link between cocaine-induced cerebellar plasticity and the development of sensitisation has not been demonstrated thus far (Vazquez-Sanroman et al., 2015b). Additionally, future studies need to test whether cocaine-dependent cerebellar plasticity is required for the persistence of cocaine-induced sensitisation observed after long withdrawal periods.

4. The cerebellum is crucially involved in the formation and long-lasting storage of Pavlovian emotional learning.

The ultimate goal of pavlovian associative learning is to optimise the efficacy and to tune behavioural responses to environment by anticipating the triggering of motor and vegetative reactions. Human and animal research has shown the cerebellum to be crucially involved in the acquisition and consolidation of different forms of associative motor learning including classical eyeblinking conditioning and compensatory eye movement reflex (vVOR) (Thompson and Steinmetz, 2009; Galliano et al., 2013). The cerebellum appears to contribute to associative learning separately from its participation in motor functions. In fact, patients with cerebellar injuries and other serious cerebellar conditions show deficits in associative learning tasks that

are not affected by manipulations of motor demands (Timmann et al., 2010).

The cerebellar role in aversive emotional learning is, however, more relevant for the present discussion (Sacchetti et al., 2002; Sacchetti et al., 2005). It is known that cerebellar dysfunction alters vegetative and behavioural conditioned fear responses (Supple and Leaton, 1990). Reversible inactivation of the cerebellar cortex after conditioning sessions prevents the consolidation of cue- and context-induced fear conditioning without affecting unconditioned response (Sacchetti et al., 2002). Moreover, electrophysiological records performed in slices from animals previously trained in fear conditioning demonstrated a selective potentiation of the response (LTP) in Purkinje-parallel fiber synapses of lobules V-VI (Sacchetti et al., 2004). Clearly, this seems to be related to the formation of new memories because it was not evident in the unpaired group. Interestingly, *hotfoot* mice, showing a selective deficiency in GluRδ2 subunits in Purkinje-parallel fiber synapses, exhibit retention impairments of short and long-term cue-induced aversive conditioning (Sacchetti et al., 2004). In motor Pavlovian learning conditioned (CS) and unconditioned stimuli (UCS) reach the cerebellum through dissociated pathways (Thompson and Steinmetz, 2009). CS signals convey to the cerebellar cortex via mossy fibers. However, UCS neural information does this from the inferior olive through climbing fibers. In fear conditioning plastic changes only affect parallel-Purkinje synapses (Sacchetti et al., 2004). So, it has been suggested that different afferent channels of mossy fibers arising from the pontine nuclei would convey both CS and UCS to the cerebellar cortex (Strata et al., 2011). Emotional associative memory appears to be localized in the posterior cerebellar cortex. An unconditioned painful experience activates the anterior vermis whereas a cue signalling a subsequent painful stimulation increases activity in the posterior cerebellum (Ploghaus et al., 1999).

Consequently, the role of the cerebellum appears to be crucial to long-lasting storage of CS-UCS relationships. This suggestion seems to be coherent with the role of the cerebellum in predictions about internal events related to external cues (D'Angelo and Casali, 2013). Thus, the

cerebellum would accomplish prediction in order to elicit preparatory operations in the brain networks that are needed to respond to the upcoming events. In this way, the cerebellar cortex would be in charge of rapid unconscious processes, while other cortical brain areas would address the slow conscious ones (D'Angelo and Casali, 2013).

5. Drug-related cue memories also involve the cerebellum.

Pavlovian conditioning tunes the motivational drive for drug-associated stimuli, fostering the probability of those environmental stimuli to promote and trigger drug seeking and taking. The permanent capability of these cues to trigger drug consumption derives from an over-consolidation of such drug-dependent Pavlovian memories (Everitt and Robbins, 2005). Evidence arising over the last three decades has shown that long-lasting plastic modifications in the corticostriatal-limbic circuitry underlie the long-term durability of drug-related conditioned memories (see Everitt, 2014 for a recent review). Moreover, drug-induced progressive increase in dopaminergic activity stimulates a ventro-dorsal reorganization of these loops promoting the escalation of drug intake (Willuhn et al., 2012).

For years, the cerebellum has been a neglected region in brain circuits holding these long-lasting drug-related memories. This is surprising because several decades of research have demonstrated that the cerebellum mediates consolidation of Pavlovian memories as formerly discussed. Together with this, numerous human neuroimaging studies in cocaine addicts and alcoholics have shown cerebellar activations during exposure to drug-associated cues (Grant et al., 1996; Schneider et al., 2001; Bonson et al., 2002; Anderson et al., 2006; for a recent review see Moulton et al., 2014). Perception of the paraphernalia associated with cocaine intake increased activation of the dorsolateral prefrontal cortex, the amygdala, and the cerebellum (Grant et al., 1996). Later on, Bonson and coworkers (2002) found that when cocaine addicts listened to an evocative script describing physiological and psychological sensations associated with cocaine use, the right cerebellum was also activated. Other results showed that cocaine-associated cues elicit regionalized activation in lobules II, III, VIII, and IX of the vermis

(Anderson et al., 2006). Similar findings have been described during olfactory stimulation with ethanol in alcoholic patients under detoxification. Craving-elicited odour cues activate the right amygdala, hippocampus, insula and cerebellum (Schneider et al., 2001). After 3 weeks of therapeutic intervention patients exhibited reductions in subjective craving, accompanied by normalization in their cerebellar activity. It is compelling that in all these studies cerebellar activations were not observed when subject were presented with neutral cues. Importantly, it precludes the consideration of cerebellar activity as merely resulting from stimulus perception.

Expectations of reward are a pivotal cognitive process mainly derived from drug-induced learning based on Pavlovian conditioning. It is the cue-elicited expectation of drug availability which triggers drug seeking and taking. Remarkably, cerebellar activations have also been linked to drug-associated expectations. When cocaine addicts expected to receive a drug dose and then received it, cerebellar and thalamic glucose metabolism were higher than when they expected placebo and then actually received the drug; or expected the drug and received the placebo (Volkow et al. 2003). Hence, cerebellar activation was greater if expectations were fulfilled, but decreased when predictions were inaccurate. The self-reported feeling of a "high" was also larger when expectations were generated, but in this case there was no correlation with any cerebellar activity. Accordingly, when relapse has been investigated, heroin *relapser* patients as compared to healthy subject and *non-relapsers* show significantly greater cue-induced brain response in the bilateral nucleus accumbens (Nac)/subcallosal cortex and cerebellum. However, only Nac activity correlates with feelings of craving (Li et al., 2014). Overall, data from human samples of drug addicts fit very well into the functional perspective proposed for the cerebellum by D'Angelo and Casali, (2013). Thus, it seems that cerebellar function is mainly to do with an unconscious prediction process of drug availability, rather than with the generation of drug-associated conscious feelings of craving.

Recent research from our lab has tackled a further characterization of the cerebellar involvement in drug-induced preference conditioning (Carbo-Gas et al., 2014ab). We have found a specific

and distinctive cerebellar hallmark of preference for cues linked to cocaine experience. When an animal expressed a preference towards an odour associated with the drug, we observed an increase in cFOS expression in the dorsal region of the granule cell layer- mostly in granule cells. This distinctive feature was not seen if animals did not exhibit conditioned preference. This happened no matter whether they were trained contingently but never expressed conditioned preference (the non-conditioned group) or merely treated in an unpredictable way with cocaine (the unpaired group). In both cases, this cerebellar signature was not seen. Furthermore, the cerebellar patterns of cFOS expression in the unpaired group were completely different from either the conditioned or the non-conditioned group. Unpaired mice showed the lowest cFOS expression in the granule cell layer as compared to the saline, conditioned and non-conditioned groups. Rather, the two brainstem sources of cerebellar inputs, the inferior olive and the pontine nuclei, as well as the medial nucleus, the output of the vermis, exhibited the highest levels of cFOS expression. Through this evidence, it seems that neurons in the input and output nuclei of the vermis increase their activity when prediction is not possible and then the suitable behavioural alternative for the current contextual situation is unforeseeable (Carbo-Gas et al., 2014b).

Interestingly, the cerebellar signature of cocaine-dependent preference conditioning was found throughout the anterior and posterior vermis. Nevertheless, the expression of preference only correlated with cFOS levels in lobule III and VIII (Carbo-Gas et al., 2014ab). The involvement of lobule VIII deserves special attention. On the one hand, lobule VIII is one of the components of the sensorimotor network (Schmanhmann, 1991; Bostan et al., 2013). On the other hand, the posterior vermis has been proposed as “the limbic cerebellum” (Turner et al., 2007; Timmann et al., 2010; Strata et al., 2011; Bostan et al., 2013). Therefore, lobule VIII exhibits an advantaged position when carrying out predictions using drug-related cue memories in order to evoke preparatory operations in the brain motor networks that automatically trigger drug seeking. Accordingly, it has been involved in automatizing behavioural repertories toward drug-related

cues (see Yalachkov et al., 2010 for a review).

An important issue that remains unexplored is the question of through which pathways CS and US signals reach the cerebellar cortex. One can speculate that CS odour information arrives at the cerebellum from the medial amygdala and orbitofrontal cortex via mossy fibers originating in the pontine nuclei. Both brain regions are key components of the olfactory system and sustain odour reward memories (Tronel and Sara, 2002). Unconditioned effects of drugs include a complex layout of interoceptive and central signals. Thus, during drug-dependent conditioning UCS information could end up at the cerebellum not only from both the pontine nuclei and the inferior olivary complex, but also cocaine may impact directly on cerebellar molecular targets.

6. Instrumental memory and executive functions recruit prefrontal-cerebellar circuits.

Habits can be defined as learned, repetitive, sequential behaviours being performed in relation to a preceding goal and the antecedent behaviour that most successfully leads to attaining that goal (Graybiel, 2008). During acquisition of habits, there is a shift from a kind of behaviour regulated by an action-outcome process to simpler cue/context triggered behaviour (Graybiel, 2008). This behavioural tuning involves brain networks underpinning Pavlovian and procedural rewarded learning as well as decision-making. Drug-related cues drive goal-directed behaviours towards contexts with drug availability. With extended drug experience a discrete series of goal-directed actions to obtain the drug are assembled in a coherent sequence and behaviour becomes habitual and automatized. Of note, drug-induced habit formation has been proposed as a key feature in the transition to addiction (Everitt and Robbins, 2005).

Interestingly, several data provide evidence of cerebellar contribution to repetitive sequential learning and habit formation. Brain imaging research in normal human samples reveals cerebellar deactivations during the automatic phase of sequential learning (Wu et al., 2004; Doyon and Benali, 2005; Balsters and Ramnani, 2011). Both the prefrontal cortex and cerebellum reduce their activity as sequential learning progresses. Then, if task demands increase prefrontal cortex activity is engaged again but the cerebellum remains deactivated

(Doyon and Benali, 2005). These findings parallel results from electrophysiological recordings performed in the cerebellar cortex of rodents during motor learning. In these studies, the initial learning phase is characterized by high cerebellar cortical activity, which decreases with trials and repetition (De Zeeuw and Yeo, 2005; Garcia-Martinez et al., 2010). So, the prefrontal cortex and cerebellum work in parallel during acquisition and progression of learning but they are recruited in a competitive manner when cognitive and motor demands grow.

Clinical studies have suggested skill-learning impairments (Mulhern et al., 2004) and decision-making deficits (Cardoso et al., 2014) occur after cerebellar injury. However, hemicerebellectomy rather than preventing acquisition of sequential learning seems to delay the transition to response automatisation (Mandolesi et al., 2010). Moreover, a bilateral lesion in the interpositus nucleus prevents rats from developing habits with overtraining (Callu et al., 2007). In these rats, behaviour maintains the action-outcome features and transition to the automatic cue-response stage is not created. However, the lesion does not affect any learning process of an instrumental task (Callu et al., 2007). Therefore, contrary to correlational findings lesion studies suggest that the integrity of the cerebellum is not critical to learning goal-directed behaviours, but it is a hub of the brain process underlying habit formation.

Another issue worthy of consideration is the dissociation in the behavioural consequences of cerebellar lesions. While interpositus impairment prevents the emergence of habits, lesions of the posterior cerebellar cortex cause deficits in executive function and affective dysregulation. As a matter of fact, posterior vermis lesions result in a delay in behavioural inhibition during extinction trials, rather than hamper the development of automatic responses (Callu et al., 2007). Accordingly, the vermis appears to be relevant to perseverative behaviour and behavioural inhibition (Bobée et al., 2000). Animals that received vermix lesions when young showed perseverative behaviour as adults, lack of attention to novel stimuli and behavioural disinhibition. This is a behavioural phenotype very similar to those rats that fulfil addiction criteria (Deroche-Gamonet and Piazza, 2014). Overall, clinical data suggest that lesions and

pathological conditions reorganize prefrontal-cerebellar network functions.

Certainly, this is what seems to occur in addicted subjects. Cocaine addicts and alcoholics exhibited non-responsiveness of the anterior cingulate cortex and other prefrontal regions accompanied by over-responsiveness of the cerebellum when cognitive task demands increased (Desmond et al., 2003; Hester and Garavan 2004; Goldstein et al., 2007). However, normal subjects had the expected pattern of brain activity, i.e. prefrontal over-activation together with cerebellar deactivation. Moreover, abstinent rhesus macaques with a history of cocaine self-administration for a year showed greater metabolic activity in the cerebellum but lower levels in the prefrontal cortex during performance of a working memory task (Porter et al., 2014). Similarly to cocaine and alcohol addicts, the brain of marijuana abusers expresses lower activation in the orbitofrontal and dorsomedial cortices but over-activation in the cerebellum while they are playing the Iowa Gambling Task (IGT). This brain pattern correlates with hypersensitivity to immediate rewards (disadvantage cards) and less sensitivity to losses (Bolla et al., 2005). Nevertheless, in other studies both the medial prefrontal cortex and cerebellum show greater activity during the performance of the IGT (Vaidya et al., 2012). The main difference between these two studies is regarding the withdrawal time. It was very short (24h) in the Vaidya study and much longer (25 days) in the Bolla report. So, apparently, the length of the abstinence period seems to be a relevant variable to take into account in order to properly explain prefrontal-cerebellar functional relationships in the addicted brain.

Interestingly, brain regions controlling tool use skills and action knowledge increase their activity when drug-related cues are presented. Thus, smokers showed higher activation than non-smokers in the right lateral cerebellum, the left premotor cortex and, the left superior parietal lobule during the presentation of smoking-related cues (Yalachkov et al., 2009). On the other hand, smokers show more restrictive brain activity patterns than non-smokers during a reward task. Either monetary or nonmonetary rewards increase activity in the cerebellum exclusively in smokers. In non-smokers the brain pattern was wider, involving the striatum,

prefrontal cortex and limbic cortices (Martin-Sölch et al., 2001).

On the whole, a sort of prefrontal-cerebellar competition can be observed in both addicted subjects as well as normal samples when task demands increase but this is expressed in a reverse manner. In addicts, during the performance of high demanding tasks over-activity is seen in the cerebellum together with non-responsiveness in prefrontal cortices. Hence, it seems that in drug addicts and heavy drug users the cerebellum controls functions normally tackled by the prefrontal cortices. Nevertheless, the cerebellum does not produce a behavioural flexible executive control, but a rapid and automatic one. Perhaps, this may partially explain why addicts show perseverative behaviour and impairment in executive functions (Miquel et al., 2009).

7. Neuroimaging findings support structural cerebellar alterations that might be a part of the endophenotype of addiction

Overall, neuroimaging findings have demonstrated structural alterations in the cerebellum of addicts (see for a review Moulton et al., 2014). Global cerebellar gray matter of cocaine addicts (Barrós-Loscertales et al., 2011), alcoholic patients (Segobin et al., 2014) and heavy smokers (Yu et al., 2011) exhibit reduced volume as compared to control individuals. In addition, disruption of connectivity has been described in the cerebellar peduncules, formed by cerebellar afferent and efferent projections (Bora et al., 2012).

However, to date it is not clear whether these cerebellar abnormalities are part of the addiction endophenotype; result from injuries and alterations during development; or are the consequence of brain toxicity after a prolonged experience with addictive drugs. Remarkably, subjects who are members of high-risk families of alcoholic and psychostimulant addicts (who do not take drugs) showed localized greater cerebellar gray matter volumes (Hill et al., 2011; Ersche et al., 2012). This specific increase has also been found in heavy marijuana users (Medina et al., 2010; Cousijn et al., 2012; Battistella et al., 2014). The interesting thing is that this gray matter increase was not related to the age of first use or the extent of cannabis consumption

(Battistella et al., 2014). In normal development, cerebellar gray matter decreases progressively from puberty until early adulthood (Diamond, 2000; Ostby et al., 2009) due to the pruning of synaptic connections (Cohen-Cory, 2002). Thus, this cerebellar feature identified in addict cohorts and their relatives could derive from an atypical pruning (Battistella et al., 2014) during development or it might be linked to the addiction endophenotype, given that this structural signature has been also found in relatives of addict cohorts.

The final structure and functionality of the cerebellum take a long time to be fully developed, making cerebellar circuitry susceptible to alteration by a plethora of different external and internal events at different developmental stages (Koziol et al., 2014). More importantly, cerebellar impairments during very early periods of life have the capacity to shape mature brain structure and functions (Limperopoulos et al., 2014). Furthermore, cerebellar pathology can contribute to prefrontal dysfunction. For example, several studies suggest that cerebellar injuries during perinatal/postnatal stages are sufficient to produce alterations in distal cortical areas (see Wang et al., 2014 for a review). Accordingly, cerebellar damage has been associated with a reduction in the modulation of dopamine release in the medial prefrontal cortex as well as with a reorganization of cerebello-cortical loops (Rogers et al., 2013).

Growing evidence links abnormalities in the cerebellum with those neuropsychiatric disorders that show comorbidity with addiction, including schizophrenia (Leiner et al., 1986; Andreasen et al., 1998; Konarski et al., 2005; Yeganeh-Doost et al., 2011) and attention-deficit hyperactivity disorder (ADHD) (Pastura et al., 2011) (see Villanueva, 2012 for a recent review). The key symptomatology in these mental disorders goes beyond the mere sphere of motor dysfunction, essentially affecting integrative processes under control of prefrontal-thalamic-cerebellar loops (Koziol et al., 2014). Structural and functional alterations in these circuits are believed to result from dysfunctions of normal CNS development (Weinberger, 1987; Conti et al., 2015) due to environmental factors or genetic polymorphisms. Currently, it is widely accepted that comorbidity between mental disorders is the final manifestation of shared

physiopathology and risk genes (Hyman, 2007). By way of illustration, 27% of top candidate genes for schizophrenia are present in alcoholics (Levey et al., 2014). Importantly, similar prefrontal-cerebellum abnormalities have been described in autism (Allen et al., 2004; Fatemi et al., 2012; Rogers et al., 2013; Skefos et al., 2014), which is a mental disorder that has not shown comorbidity with drug addiction but with Internet addiction (Mazurek and Engelhardt, 2013). Nevertheless, prefrontal and cerebellar alterations in patients suffering of these mental disorders do not seem to resemble what has been observed in the relatives of addicts. On the contrary, in these patients, neuroimaging studies have found a reduction in the number of neurons and lower prefrontal and cerebellar activity (Andreasen et al., 1999; Nopoulos et al., 1999; Allen et al., 2004; Scott et al., 2009; Koziol et al., 2014; Edmonson et al., 2014; Murphy et al., 2014; Osipowicz et al., 2015).

In summary, it is still a matter of conjecture whether these structural and functional findings, previously described in prefrontal-cerebellar networks, could result from chronic drug use or could also reflect a genetic risk factor of addiction (Moulton et al., 2014).

A hypothetical conceptual framework for the cerebellum's role in addiction

We started this review by asking whether there were other relevant brain regions involved in addiction beyond the corticostriatal-limbic circuitry. We hope to have been able to provide compelling evidence to challenge the traditional point of view about the neuroanatomy of addiction and encourage the inclusion of the cerebellum in this circuitry.

All the data discussed in the present review regarding the involvement of the cerebellum in addiction have been obtained using a correlational approach. **To our best knowledge, there is not any published data about the causal involvement of the cerebellum in drug addiction**. **Correlational studies** have led to the conclusion that addictive drugs induce and persistently modify plasticity mechanisms in the cerebellum. However, it is clear that being affected by addictive drugs might not be sufficient to support the inclusion of the cerebellum as part of the addiction circuitry. Further causal studies affecting cerebellar integrity and its activity are

required in order to integrate undeniably the cerebellum in these brain networks. Such studies should explore different addiction-related processes, but must also include animal models of addiction such as drug self-administration experiments at different stages of the transition from recreational drug consumption to an addictive pattern of behaviour. Furthermore, future studies should also establish whether the cerebellum's role is specific for drug addiction requiring drug-induced changes in cerebellar plasticity; or they could be generalised to all behavioural addictions. Interestingly, an increase in cerebellar activity has been observed when cocaine addicts are exposed to both food and cocaine related cues (Tomasi et al., 2015). Thus, cocaine heavy users over-activated the cerebellum during the observation of food- and cocaine-related videos as compared to neutral videos. Moreover, the functional connectivity between the cerebellum and one of the key structures of the reward system, the ventral striatum, increases in pathological gamblers (Koehler et al., 2013). These findings suggest a global involvement of the cerebellum in addiction disorder.

Our lab is currently investigating the effects of focalised or combined prefrontal and cerebellar lesions on cocaine-induced preference conditioning. The preliminary findings showed that the effects on the acquisition of a preference towards an odour-cue associated with cocaine depended on the exact placement of the lesion (Gil-Miravet et al., 2015). Either a lesion at the dorsal region of lobule VIII performed previously to conditioning training, or a deactivation of the infralimbic cortex before every conditioning trial promoted cocaine-induced preference conditioning. After either of these lesions, 100% of the animals expressed a preference towards the cocaine-related cue, but only 45% of the sham group did. Remarkably, combined lesions precluded the effect of the separate lesions. Conversely, lesions placed ventrally in the granule cell layer of the vermis or prelimbic cortical deactivations prevented the acquisition of cocaine-induced preference conditioning. Our results regarding the effects of the prefrontal cortex are partially in agreement with other previous findings that demonstrated a differential involvement of prelimbic and infralimbic regions in cue-induced reinstatement of drug seeking. The prelimbic impairment has been demonstrated to prevent cue, drug or stress-induced

reinstatement of drug seeking (McFarland and Kalivas, 2001; Capriles et al., 2003; Ball and Slane 2012). On the other hand, infralimbic deactivations facilitated reinstatement after extinction (Peters et al., 2008). It seems that prelimbic and infralimbic prefrontal regions form different functional loops with the NAc and basolateral amygdala in order to trigger drug seeking or exert an inhibitory control over it (Gipson et al, 2014).

One of the roles ascribed to the cerebellum is related to behavioural inhibition (Picazio and Koch 2015). Evidence to support this suggestion derives from lesion and transcranial magnetic stimulation (TMS) studies in humans (Schmahmann et al., 1998; Tanaka et al., 2003; Brunamonti et al., 2014). Overall, a lack of behavioural inhibition has been observed after cerebellar lesions (Schmahmann et al., 1998; Tanaka et al., 2003). Conversely, increased activity in the cerebellum correlated with an improvement of inhibitory control (Brunamonti et al., 2014). Nevertheless, regular cocaine users, who showed lower prefrontal activation and bad performance during an inhibition task, also exhibited an over-reliance on the cerebellum (Hester and Garavan 2004). Moreover, our recent findings point to a more complex landscape in which functionally segregated corticostriatum-limbic-cerebello networks with opposite roles would be involved in behavioural executive control.

Taking together all of these findings, a hypothetical working model of the cerebellum's role in drug addiction is proposed (Figure 3). In this model, different regions of the cerebellar vermis (see Figure 1) would be part of different functional corticostriatal-limbic loops (Figure 3). Consequently, neurons in **the dorsal region of the posterior cerebellar vermis** would be linked to the infralimbic region, NAc shell, basolateral amygdala in order to inhibit drug seeking after drug-associated cue presentation. In contrast, those neurons in the ventral posterior region of the cerebellar cortex appear to be related functionally to the prelimbic cortex and NAc core circuitry, which sustains drug seeking. Moreover, as we suggested previously (Miquel et al., 2009), the relevance of the cerebellum in addiction is expected to be greater to the extent that the prefrontal cortex activity is reduced during the

transition from goal-directed drug seeking to a compulsive phenotype.

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Figure 1. Anatomical organization of the rat cerebellar cortex Different anatomical and functional regions are depicted in a sagittal section of the cerebellar vermis. Cerebellar lobules are identified by Roman numerals. ML: Molecular layer; PL: Purkinje Layer; GL: Granule cell layer.

Figure 2. The cerebellar circuitry The cerebellar cortex receives two excitatory inputs, the mossy fibres (MF) originated in the pontine nuclei and the climbing fibres (CF) projecting from the inferior olive. The main targets of MF are Golgi interneurons and granule cells within the glomerulus. In the glomerulus, complex excitatory and inhibitory synaptic relationships control the final convergent glutamatergic output from granule cells to Purkinje neurons, which are gabaergic neurons. These two afferents segregate onto Purkinje dendrites creating different functional domains. Parallel fibres limit their contacts to the distal dendrites, whereas climbing fibres synapses are restricted to the proximal zone of the Purkinje dendritic tree. In addition, climbing and mossy fibres send direct excitatory inputs to the DCN. Also, DCN include GABAergic neurons, which in turn regulate the activity of these two cerebellar afferent pathways. Although still controversial, the most accepted functional scenario is that the temporal association between the activity of climbing and parallel terminals onto Purkinje dendrites results in long-lasting modifications in Purkinje spiking, which leads to a disinhibition of the DCN. Larger glutamatergic DCN neurons project to cortical and striatal regions through the different thalamic areas.

Figure 3. A hypothetical model for the cerebellum's role in addiction In this hypothetical model, different regions of the cerebellar vermis would be part of segregated functional corticostriatal-limbic loops with opposite roles in drug seeking. On the one hand, **the dorsal region of the posterior cerebellar vermis** is linked functionally to the infralimbic region, NAc shell and basolateral amygdala in order to promote extinction memory and to inhibit drug seeking after drug-associated cue presentation. On the other hand, those neurons in the ventral posterior region of the cerebellar cortex appear to be related functionally to the prelimbic-NAc

core circuitry, which promotes cue-induced drug seeking (see Gipson et al., 2014 for a recent review of corticostriatal-limbic interactions).

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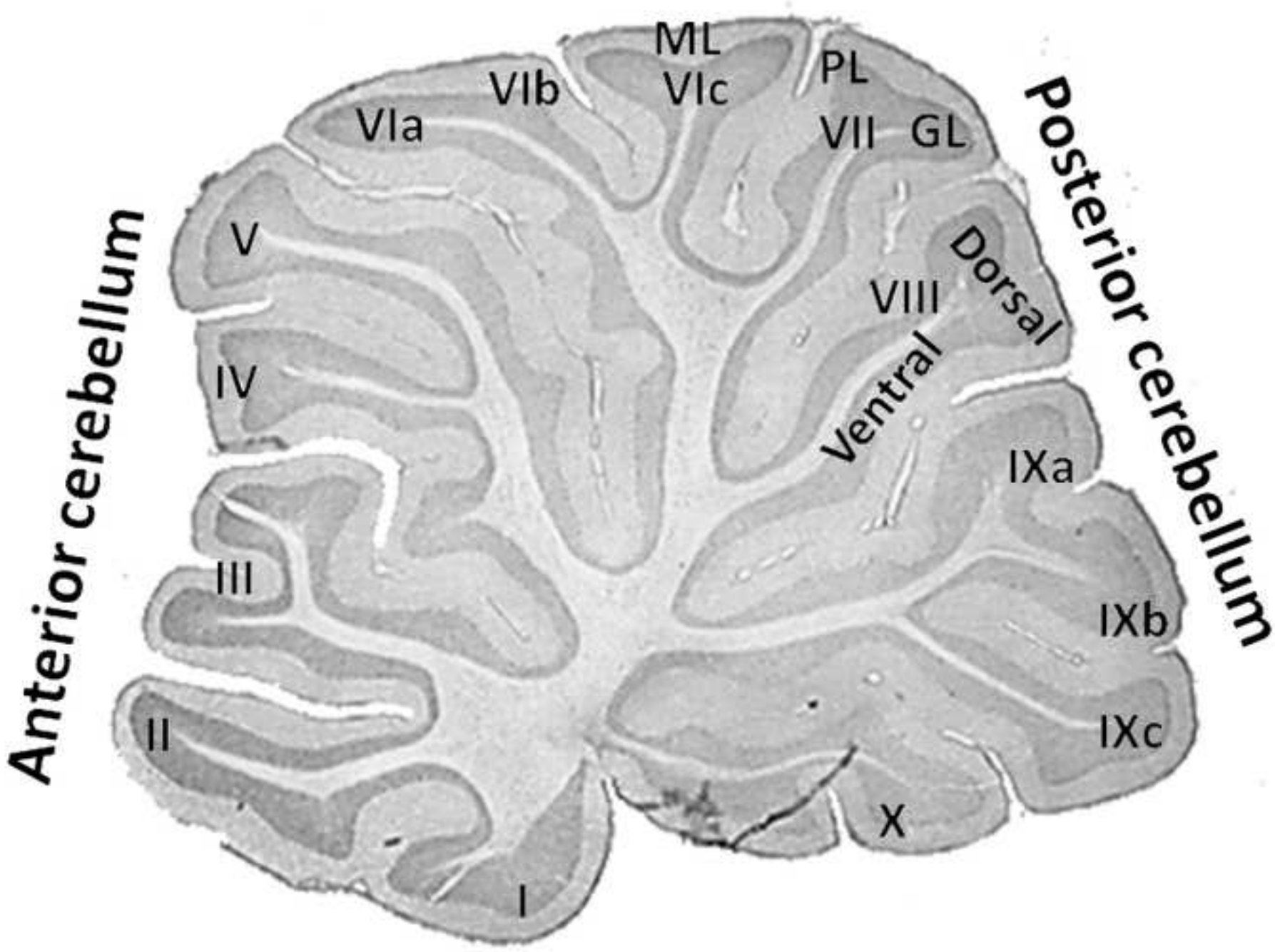

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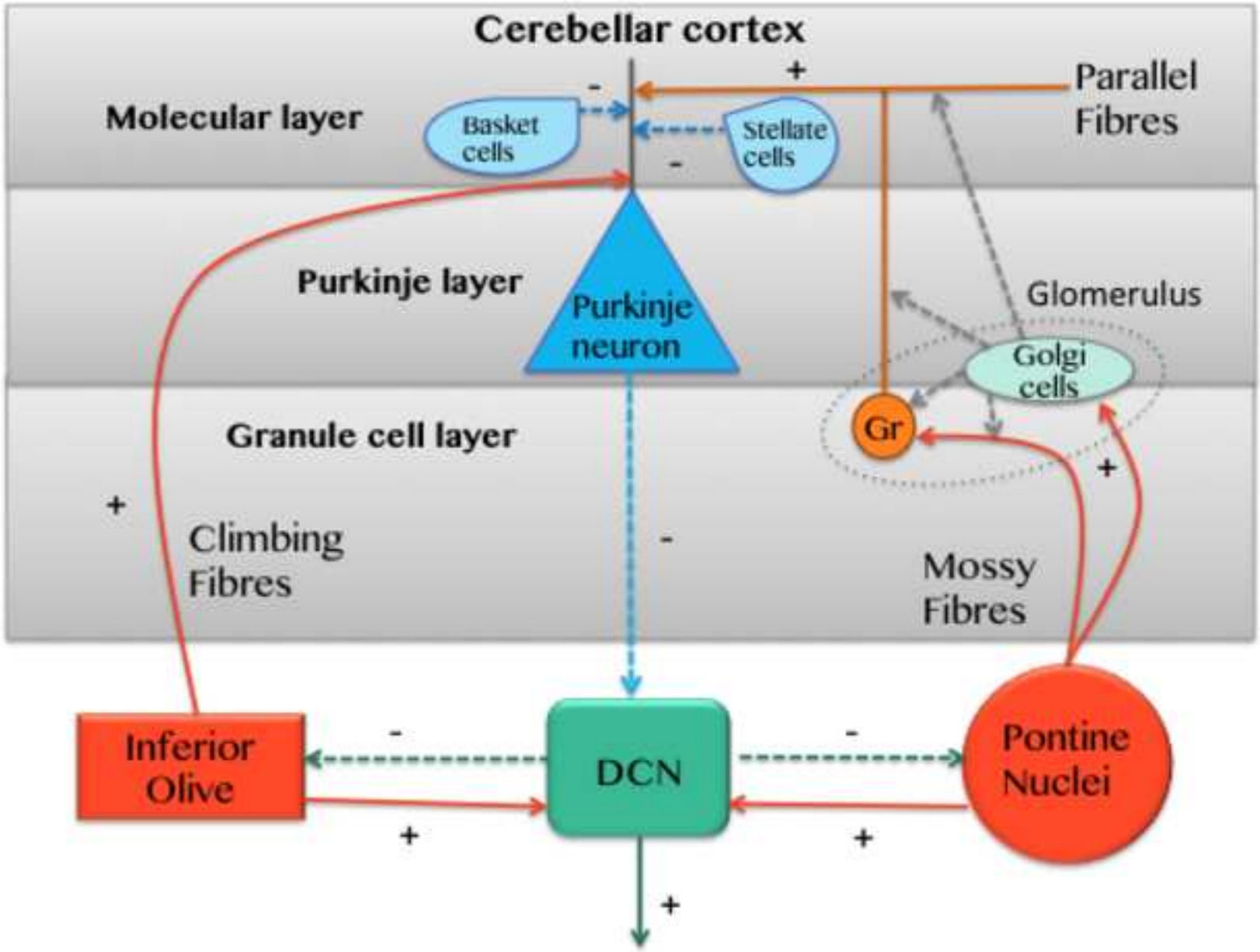

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